

Neurological point of view Bacterial spondylodiscitis: diagnostic challenges and therapeutic strategies

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Abstract

Spondylodiscitis has gained attention lately because of an alarming and progressive increasing of its incidence, reflecting the rise of percentage of the elderly and immunocompromised people, and the implementation in practice of advanced diagnostic methods. This review will focus on the etiology, diagnostic challenges, and treatment strategies in spondylodiscitis. The incidence of spondylodiscitis is currently 4-24/1 million, making up to 3-5 % of total osteomyelitis cases. It is approximately two times more common in men than in women. *Staphylococcus aureus* is involved in 48 % - 62.5 % of cases of spondylodiscitis. The clinical picture is dominated by spinal pain and stiffness, and increased erythrocytes sedimentation ratio and C-reactive protein are laboratory markers of spondylodiscitis. The most sensitive imaging method is magnetic resonance imaging. Bacteriological examination is very important for proper and effective treatment, guiding the selection of the antibacterial regiment that has proven to be effective in about 75 % of patients. In other cases, surgical treatment may be used. The prognosis is favorable, except for those with comorbidities or noncompliance with treatment.

Key words: spondylodiscitis; discitis; disc infection.

Introduction

Infection of the intervertebral disc is a little studied problem, and which endangers in a significant extent the health and quality of life of patients if untreated. In the reason of a quasi-permanent association of the vertebral body inflammation, to define the disk infection further, “spondylodiscitis” term will be used. Spondylodiscitis has gained attention lately because of an alarming and progressive increasing of its incidence, (1) reflecting the rise of number of the elderly and immunocompromised people, and the implementation in practice of advanced diagnostic methods. The absolute number of spondylodiscitis cases also increases progressively in close accordance with the raise in the number of spine interventions. (2) Non-specificity of the clinical picture, clinical setting of appearance and the unfamiliarity of medical staff with this disease, often exclude spondylodiscitis from clinical reasoning of neurologists. (3) Delayed diagnosis can have disastrous consequences for the patient, disability and permanent deformation of the spine being the possible scenario. The management of

spondylodiscitis is also a subject of many controversies incited by the absence of clinical guidelines and treatment protocols.

The incidence of spontaneous infectious spondylodiscitis has a bimodal distribution with peaks at ages under 20 years and in people after age of 50 years, (1) global values of incidence in developed countries varying in the range of 4-24 to 1 million populations (3) and make up from 3 % to 5 % of the total number of osteomyelitis. (4) The distribution by sex reflects a slight prevalence in men, their ratio to women being 1,5:1 (5, 6) or 2:1. (7, 8) The mean age of patients with postoperative spondylodiscitis tends to be lower than that of patients with spontaneous spondylodiscitis (60-69 versus 46-52 years). (7-9)

Spondylodiscitis is an inflammation of the intervertebral disc and neighboring vertebrae. The sequence of involvement in the process of these structures depends largely on their anatomical structure, chemical composition, and vascularization. There are three possible scenarios for the development of spondylodiscitis: primary infection of intervertebral disc by hematogenous spread of bacteria, vertebral body primary infection, or direct inoculation of the pathogen in the disc. The first mechanism is characteristic for spondylodiscitis in children, the rich vascularity of the intervertebral disc contributing to the precipitation of the pathogen at this level, often the infectious process being limited to this area, in which case we talk about pure discitis. Also, such a development of the events may be possible in the elderly, (10) where the disc capsule, by virtue of degenerative processes, becomes vulnerable to microbial invasion. The second scenario is observed in adults.

In such cases the intervertebral disc is largely avascular, and vascularization of the lamina terminalis has already begun to suffer from loss of intraosseous anastomoses, so that it creates the possibility of a primary infection of subchondral bone, which by destroying the lamina terminalis will propagate to adjacent intervertebral disc. (11) Infection by direct inoculation is seen in iatrogenic spondylodiscitis. The propagation of germs in hematogenous spondylodiscitis can occur via arterial flow and, rarely, venous circulation. The source or site of entry of the infection is most often the skin (21 %), followed by the genitourinary (10 %) (5) and intestinal (12) tracts. However, in 53 % of cases of infection the site of entry remains unidentified. (5)

Diagnostic challenges

The spondylodiscitis diagnosis rate at first visit to the physician is discouraging small, reaching only 39 % of cases. (5) Given the non-specificity and nebulosity of symptoms at onset, the most common destination of visits of patients with spondylodiscitis is primary care units (66.7 %). (13) As a result, diagnostic failure worsens because of unawareness and reduced vigilance of physicians for this disease. The same is true for endocrinologists who have the mission to fight the prevailing background of spondylodiscitis - diabetes mellitus. The time between the start of symptoms and the establishment of diagnosis in different studies ranged from 2 days to 12 months, (9, 14, 15) with an average of 4.3 months, (16) being higher in patients with postoperative spondylodiscitis. (8)

One explanation is the similarity of clinical (pain) and laboratory (erythrocytes sedimentation rate (ESR), C-reactive

protein (CRP)) markers of spondylodiscitis and the normal postoperative changes. (17) Achieving ESR peak at day 5 of surgery and returning to normal in the first 3 weeks is a normal postoperative dynamic and any digression from this rhythm would raise suspicion. (18) Given the prompt dynamic of changes of C-reactive protein (peak at day 3 and returning to normal in the first 2 weeks), this parameter may be more useful than ESR in detecting early deviations from normal postoperative course. (18) In addition, the presence of neurological deficit in patients with spondylodiscitis increases confusion by directing the clinical reasoning to a post-operative relapse or failure of surgery, especially in the presence of pain with radicular distribution. (19) Lack of fever in many patients with postoperative spondylodiscitis (8, 19) results in ignoring the infectious nature of observed changes. Finally, the imaging changes in spondylodiscitis can be included in the normal postoperative picture, (20) although the identification of vertebral edema on MRI has determined the usefulness of this method in differentiating between the two situations. (18)

Hazy clinical picture, slow evolution, and atypical symptoms (lack of systemic inflammatory reaction and fever) are responsible for the retard in the diagnosis of tuberculous spondylodiscitis, reaching an average of 6-8 months. (21, 22) For atypical and suspicious cases is recommended to repeat MRI over 1-2 weeks, during which specific changes of spondylodiscitis can be delineated. (B2) (10, 21)

Etiology

In the etiology of spondylodiscitis usually is involved a single organism, although multibacterial infection has been reported occasionally, especially on an

immunocompromised or diseased background. (12) The most often isolated germ has been *Staphylococcus* with a frequency of 48 % - 62.5 %. (8, 9, 23) Most of the community acquired *Staphylococci* are sensitive to methicillin and about 30-40 % of nosocomial staphylococcal infections are methicillin-resistant. (24) Next in frequency are Gram-negative bacilli (4-30 %) and streptococci / enterococci (5-30 %). (21, 25, 26) Gram-negative bacilli are commonly seen on an immunocompromised background or after infections of gastrointestinal or genitourinary tracts, (21, 24, 26) while anaerobic infections are more common in diabetic patients. (27) Fungal infections are the cause of about 1 % of non-tuberculous spondylodiscitis in adults, the leading role played by *Candida albicans* (21) and usually occur on a background prone to this type of infection such as immunosuppression, diabetes, broad-spectrum antibiotics or treatment in intensive care units. (21, 26, 28) *Brucella* gain attention in certain geographical areas such as the Mediterranean coast, where some studies have demonstrated involvement in 25-50 % of cases of spinal infection. (15, 22) The most common risk factor in developing spondylodiscitis is diabetes mellitus. (7, 13, 15) Among other contributing factors are pathological states accompanied by immunosuppression (chronic alcoholism, (7, 9) prolonged steroidal or non-steroidal anti-inflammatory drug therapy, (8) intercurrent infections etc.), cardiovascular diseases, obesity, (4) Crohn's disease, (12) cirrhosis, (29) cancer, (9) intravenous drug use (15) etc.

Clinical picture

The clinical picture of spondylodiscitis often lacks conclusiveness and sometimes is

confusing, unless pain and spinal stiffness is present. Spontaneous nonspecific spondylodiscitis develop acutely, as opposed to specific infections that determine a blurred clinical picture and has a slow evolution. (30) In the course of postoperative spondylodiscitis, one can distinguish a clinically silent period following surgery, lasting on average 21 days and ranging from hours to months. (7) Low back pain with inflammatory character (83-100 % of cases) (5, 8, 9) is the most common cause of visits to the physician, (14, 16) and sometimes is absent in patients with spontaneous spondylodiscitis. (8) The features of spondylodiscitis pain (the nocturnal character, resistant to painkillers and rest, (28) associated with morning stiffness and worsening at bed shaking – bed-shaking test (7)) has a diagnostic utility. Pain intensity is less relevant, varying from moderate to severe. (7) Pain usually is located in the affected region of the spine but can radiate into the buttocks, thighs, abdomen, or perineal region. (7) Anatomical distribution of the infection has a downward character, lumbar region being involved in 38-70 % of cases. (5, 8, 9, 31) Spinal stiffness, present in 77-100 % of cases, (5, 7, 9) aims to reduce the burden on anterior vertebral elements. (4) The systemic inflammatory syndrome is reflected by increased body temperature (observed in 50-97 % of cases), (5, 8, 9) profuse sweating, weight loss etc. The neurological deficit is present in most cases of postoperative spondylodiscitis and only in half of those with spontaneous spondylodiscitis. (8, 16) It is more common in cervical and thoracic locations of the infectious process (25) and in cases of tuberculous nature, (22) reflecting in an indirect way the causal relationship to the

formation of paravertebral collections, (13) whose frequency was found to be increased in higher segments, (25, 32) and in patients with specific infectious. (30, 33, 34)

Investigations

One of the first changed and the most faithful marker of spondylodiscitis is ESR, which proved to be increased in 98-100 % of cases. (5, 7, 15) Even if the ESR did not correlate with severity of disease, (33) the dynamics of this parameter was found to be useful in assessing the response to the treatment. C-reactive protein is a marker as reliable as ESR, some authors (35) considering it to be even more sensitive than ESR, being increased in almost all cases (7, 15) of spondylodiscitis. The dynamics of these changes is more important than their absolute value, both to monitor the patient's clinical condition and to assess treatment efficacy. So, returning to normal ESR and CRP was observed on average 21 days (7) after the initiation of a successful treatment. Leukocytosis is an inconstant parameter, with a frequency of 42-64 % of cases. (5, 25)

The simplest and most accessible method of isolation of the infectious agent is blood culture. Resultativity of blood culture is enhanced by the increased virulence of pathogens, (29) the spontaneous nature of spondylodiscitis, (8) the multiplicity of performed sowing (at least three), (A2) (4, 21) carrying out during fever peak or within 4 hours after puncture of the intervertebral disc, (26, 36) and is drastically reduced by prior antibiotic drugs therapy, in which cases is recommended to postpone the sampling for at least 2 weeks after cessation of antibacterial therapy. (A3) (21) Given the low success rates of haemoculture in postoperative spondylodiscitis, (7) SPILF guideline

recommends disco-vertebral biopsy in any suspicions of spondylodiscitis after intradiscal surgery. (A2) (21) Urine, sputum, and samples from any site of entry are needed to detect possible sources of primary infection. (37) Three successive failed inseminations is an indication for the use of disc puncture. The procedure is done under anesthesia and radiological (computerized tomography) guidance, (4) with a success rate of 60-70 %. (14, 26, 35, 38, 39) Like blood culture, the disc puncture is compromised by prior antibiotic therapy. (21, 24) To increase the quality of the collected material, multiple sampling is recommended, two of the top terminal lamina, two of the bottom one and two from the intervertebral disc. (21) If the first disc puncture proves to be negative, it is recommended to repeat the procedure. (6, 40) Open biopsy is necessary if percutaneous puncture and empirical treatment have both failed (28). Serological investigations are not recommended to be performed routinely given their low success rate. (24)

Imaging

1. Radiography

Usefulness of radiography in diagnosing spondylodiscitis in overall is low, and lies in highlighting the pinching of the intervertebral space and progressive subchondral sclerosis in association with an increased adjacent bone density, (33) which in the later stages can pass into geodes, compressions or vertebral collapse. Broadening of the psoas shadow, mediastinum or retroperitoneal space is a sign of spreading of the infection to paravertebral tissues. (27)

2. Computerized tomography

In the first 2 weeks in 50 % of patients

(21) computerized tomography (CT) reveals pinching and hipodensity of affected disc, erosion of the vertebral lamina and the vertebral body and soft tissue edema. (36, 38, 41) (figure 1) CT usefulness is evident in guiding the disc biopsies or drainage of paravertebral collections. (37) Contrast administration will facilitate highlighting of paravertebral infiltration and fluid collection. (42)

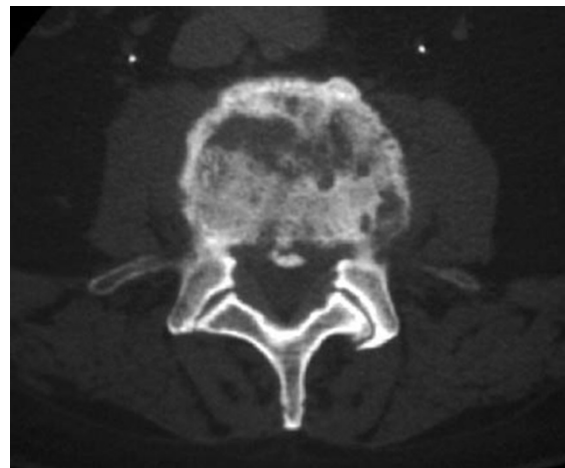


Figure 1 Computerized tomography (axial view) of the lumbar spine showing erosions of the vertebral lamina and the vertebral body. It is noticeable the sparing of the posterior elements of the vertebra

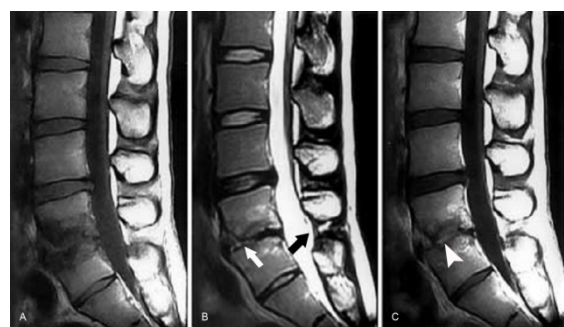


Figure 2 Magnetic resonance imaging (MRI) of the lumbar spine in a patient with spondylodiscitis: A. T1-weighted sequence showing destruction of lamina terminalis and vertebral edema; B. T2-weighted MRI revealing intradiscal hyperintensities (white arrow) and epidural abscess (black arrow); C. Contrasting of intervertebral disc (arrowhead) on contrast-enhanced T1-weighted MRI

3. Magnetic resonance imaging

Magnetic resonance imaging (MRI), considered to be the method of choice for early detection of changes in bacterial spondylodiscitis, (14, 21, 43) provides a number of criteria which are distinguished by high sensitivity and specificity: presence of epidural or paraspinal inflammation (sensitivity 97.7 %), contrasting of the intervertebral disc in T1-weighted sequences (sensitivity 95.4 %), hyperintensities or fluid signal intensities in the intervertebral disc in T2-weighted MRI (sensitivity 93.2 %) and erosions and destructions of at least one vertebral lamina terminalis (sensitivity 84.1 %). (44) (figure 2, A, B, C) Other signs include the disappearance of intranuclear hypodense slit in T2-weighted MRI, epiduritis (epidural abscess) viewed as an epidural hypointensity in T1 and hyperintensity in T2-weighted images and paravertebral abscess (T1 hyperintense and T2 hypointense signals in the lateral vertebral regions). (9) Anterior location of imaging changes in spontaneous spondylodiscitis and posterior situation of these changes in postoperative forms is a common regularity. (8) Usefulness of MRI in monitoring the progress and response to treatment of spondylodiscitis was discredited except in epiduritis and paravertebral abscess, imaging appearance of which correlated with clinical parameters and laboratory dynamics. (9) For patients in whom MRI is contraindicated (i.e. implanted pacemaker), French guidelines recommend obtaining contrast scintigraphy followed by CT. (21)

4. Other

Scintigraphy is not the method of choice, (45) while other authors consider it useful in the diagnosis of spondylodiscitis, especially in the elderly. (36) Extreme

usefulness of positron emission tomography (PET) with Fluorine-18 fluorodeoxyglucose (18-F FDG) in revealing inflammatory process in the vertebral body (4) is counteracted by the high cost of this method and the inability to differentiate between a tumor and an inflammatory process. (45)

Differential diagnosis

Differentiating spondylodiscitis from the degenerative changes of Modic I type is occasionally difficult, (46) given the similarity of imaging and clinical data. (46) Intradiscal fluid hyperintensities in T2 sequences, the erosions and destructions of the lamina terminalis, and the formation of paravertebral collections, (44) is the MRI picture that will lead us to the diagnosis of spondylodiscitis, given the rarity of degenerative origins of such changes. MRI with diffusion and F-18 FDG PET are useful in this context by revealing inflammatory changes with a hyperintense in the first case (47) and hypermetabolic in the second, (4) appearance. Coupling the imaging with the clinical (pain with inflammatory rhythm, fever, sweating) and laboratory (ESR and CRP increase) data, will increase the potential for discrimination between the two pathologies. However, one should not overlook the possibility of development of spondylodiscitis in a degenerated disc, (48) which is one of the few situations when isolated discitis can develop in adults.

The diagnosis of spondylodiscitis is sometimes evoked in the context of an injury other than infectious, such as seronegative spondyloarthritis, including ankylosing (49) and enteropathic (50) spondylitis. Spondylodiscitis developed on this pathologic background is distinguished from the bacterial variant of the disease by

the absence of a localized pain and systemic inflammatory syndrome. In addition, the anatomical location of spondylodiscitis in ankylosing spondylitis is predominantly the lower chest segment and multiple levels of injury are more commonly seen than in the analogue of bacterial origin. (49) Spondylodiscitis incidence in ankylosing spondylitis is estimated around 8 %. (49)

Treatment

1. General rules

Given the lack of prospective randomized trials, the treatment of spondylodiscitis remains controversial until today. (24) The success of conservative treatment was documented in approximately 73 % of patients with spondylodiscitis. (23) The crucial elements of a successful treatment of spondylodiscitis are the immobilization of the affected segment of the spine, antibiotics and (depending on the severity of disease) debridement and decompression of the spinal canal. (4) Targeted antibacterial treatment is a fundamental element in the management of spondylodiscitis and identification of pathogens must precede always the elaboration of an individual treatment scheme, (4) except in cases of sepsis, with critical clinical status, neutropenia or severe neurological deficit, (37) which will require the use of empirical treatment.

2. Selection of the antibiotics

In the selection of the antibiotic, its ability to penetrate bone and intervertebral disc tissue should be taken into consideration, as is well known that fluoroquinolones, clindamycin, rifampicin, fusidic acid, and metronidazole reach remarkable bone concentrations. The penetrability of beta-lactams and

glycopeptides is moderate, while aminoglycosides does penetrate bone even worse. (24) However, penetrability into the intervertebral disc correlates with antibiotic's ion charge, negatively charged antibiotics such as penicillin being far less penetrating than the positively charged ones such as gentamicin. (51) In this framework of ideas, the ability of antibiotics to diffuse in disc tissue in decreasing order is as follows: clindamycin and aminoglycosides > quinolones and glycopeptides > penicillins and cephalosporins. (51) However, the value of such data in establishing antibacterial regime is unclear, once SPILF guideline recommends as first-line treatment of staphylococcal infections penicillin and glycopeptides, (21) antibiotics that has been shown to penetrate moderately/poorly in disc tissue. (52)

Taking as support the result of bacteriologic exams, antibiotic selection within each therapeutic group will be guided by pharmacokinetic profile, ability to penetrate the disc and bone tissue, route of administration, toxicity, and cost. Thus, greater oral bioavailability will favor the selection of cloxacillin over oxacillin for the treatment per os. (53) Netilmicin was preferred among other aminoglycosides to treat infections with Gram + bacteria, since the former has less ototoxicity while teicoplanin was preferred over vancomycin because of nephrotoxicity and more complicated use of second. (54) Also, ciprofloxacin should be favored over other fluorchinolones in the treatment of infections caused by *Pseudomonas aeruginosa* or other Gram- bacteria, since it possesses the lowest minimum inhibitory concentration for these bacteria. (55) Some authors recommend metronidazole for

anaerobic etiology, (24, 56) while others plead in favor of clindamycin. (21)

3. Duration of the treatment

Duration of parenteral antibacterial therapy has been adjusted depending on the level of C-reactive protein, normalization of this parameter in the first two weeks requiring parenteral treatment cessation, or its prolongation to 3 weeks otherwise. (43) Switch to oral administration after achieving clinical improvement or normalization or considerable decrease of biological markers of inflammation (ESR, CRP, WBC) was a tactic favored by other authors. (4) Oral bioavailability of clindamycin, fluoroquinolones, rifampicin and fusidic acid is high, (57) so they are a good choice for maintenance treatment, and are not recommended for the initial treatment because of the potential for developing resistant strains. (24)

Duration of oral antibiotic treatment is from 6 weeks to 3 months for nonspecific spondylodiscitis (23) and 2 times longer, (30) typically up to one year, (15) in tuberculous cases. Paravertebral collections will sometimes require percutaneous or surgical drainage. Surgery is rarely necessary and only in cases where spinal instability, (23, 32) progressive neurological deficit, (13, 23) failure of conservative treatment (4) or cauda equina syndrome (13) are present. Antibacterial prophylaxis of spondylodiscitis is imperative after any intradiscal surgery. (58)

Prognostics

Residual symptoms may persist both after conservative and surgical treatment of spondylodiscitis. The recurrence rate of spondylodiscitis was reported to be between 0 % and 7 %. (59, 60) Adverse outcomes are related to septic complications, (16) being

more common in patients with a premorbid background such as diabetes. (31)

Conclusions

Spondylodiscitis is an issue whose importance on the one hand is often underestimated or missed and on the other hand is getting worse every year in the context of an increase in the number of spine interventions as well as in the prevalence of elderly and immune-compromised subjects. The diagnosis of spondylodiscitis is sometimes difficult, and knowledge of clinical features and atypical forms is essential for accurate and early diagnosis. At the forefront of the diagnostic labor in spondylodiscitis are imaging (MRI) and bacteriologic exams. The keystone of an effective treatment of spondylodiscitis will be always the microbiological examinations and in cases where they fail it will be adjusted depending on the most likely etiology of the disease derived from the present clinical situation and guided by the results of previous clinical studies.

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